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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,780	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/13/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 16 and 27-45 are pending. Claims 16 and 27-33 are currently under examination. Claims 34-45 are withdrawn as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement filed on 09/13/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because of the following reasons:

The Genbank Accession Numbers listed on pages 11 and 12 do not have the required dates of accession of the sequence and therefore pages 11 and 12 have not been considered. The references listed on pages 1-10 and 13-21 have been considered and signed copies have been placed in the file.

Claim Rejections - 35 USC § 102

For purposes of applying prior art, claim 1 is interpreted to mean a DFO comprising a first region having a nucleotide sequence at least partially complementary to a target RNA and having a second region having a nucleotide sequence that is an inverted repeat of the nucleotide sequence in the first region and wherein the DFO can bind to a different single stranded oligonucleotide to form a double stranded oligonucleotide.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kandimalla et al. (Nucleic Acids Research 1995, Vo. 23, No. 21" 4510-4517).

Claim 1 is drawn to a DFO as interpreted above and further limited wherein the first and second regions are separated by a palindrome sequence, wherein the DFO comprises a 3' terminal cap moiety such as a deoxy abasic moiety or a dinucleotide, wherein the DFO comprises no ribonucleotides, ribonucleotides and modified purines or pyrimidines and drawn to a pharmaceutical composition comprising said DFO.

It must be noted that the word "having" in claim 1 is interpreted as open terminology in light of the specification. Therefore, the limitation of "a first region having

nucleotide sequence complementary to nucleotide sequence of a target RNA" is interpreted to mean the first region can include other nucleotide sequences that may not be complementary to the target RNA. Likewise, the limitation of "a second region having nucleotide sequence that is an inverted repeat of the nucleotide sequence in the first region" is interpreted to mean the second region can include nucleotide sequences that are not inverted repeats of the nucleotide sequence in the first region.

Kandimalla et al. teach a single stranded oligonucleotide that is capable of forming a double stranded oligonucleotide (see Figure 2, sequence 1D). Kandimalla et al. a single stranded oligonucleotide is 19 nucleotides in length, has no ribonucleotides and comprises a region that is complementary to the gag mRNA of the HIV-1 gene (see page 4510). Kandimalla et al. teach the oligonucleotide comprises a second region that comprises sequences that are inverted repeats of a first region e.g. TCTCTC (see Figure 2). The cited sequence taught by Kandimalla et al comprises a palindrome sequence comprising 2 nucleotides that are between the first region and the second region e.g. CC (see Figure 2).

Thus, Kandimalla et al. anticipates claims 1-3 and 10 of the instant application.

Claims 1-14 and 16-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (applicant's IDS filed 09/13/2004).

Claim 1 is drawn to a DFO as interpreted above and further limited wherein the first and second regions are separated by a palindrome sequence, wherein the DFO comprises a 3' terminal cap moiety such as a deoxy abasic moiety or a dinucleotide,

wherein the DFO comprises no ribonucleotides, ribonucleotides and modified purines or pyrimidines and drawn to a pharmaceutical composition comprising said DFO.

It must be noted that the word "having" in claim 1 is interpreted as open terminology in light of the specification. Therefore, the limitation of "a first region having nucleotide sequence complementary to nucleotide sequence of a target RNA" is interpreted to mean the first region can include other nucleotide sequences that may not be complementary to the target RNA. Likewise, the limitation of "a second region having nucleotide sequence that is an inverted repeat of the nucleotide sequence in the first region" is interpreted to mean the second region can include nucleotide sequences that are not inverted repeats of the nucleotide sequence in the first region.

Tuschl et al. teach a single stranded oligonucleotide that is capable of forming a double stranded oligonucleotide CGUACGCGG**AA**UACUUGAAAUGUC (as illustrated in Figure 19, last duplex in Figure 19A). Tuschl et al. a single stranded oligonucleotide comprises a region that is complementary to a GL2 luciferase gene (see page 22) and teach the oligonucleotide comprises a second region that comprises sequences that are inverted repeats of a first region (as indicated by the underlined nucleotides). The cited sequence taught by Tuschl et al. comprises a palindrome sequence comprising 2 nucleotides that are between the first region and the second region (as indicated by the bolded nucleotides). Tuschl et al. teach 2'-deoxy thymidine, an abasic moiety, can be substituted for uridine at the 3' ends, i.e. a terminal cap. For example, the nucleotides may be modified at the 2' position of the ribose sugar on either strand, which includes any purine and pyrimidine. Preferred modifications are listed on page 6 and include 2'-

O-alkyl and 2' fluoro modifications and Tuschl et al. specifically teach the preferred modifications may be combined in a single siRNA. Tuschl et al. teach a 5'-phosphate on the antisense strand is required for siRNA function (see page 4, lines 12-20) and teach pharmaceutical compositions comprising double stranded nucleic acids and an acceptable carrier (see page 9, lines 17-25).

Thus, Tuschl et al. anticipates claims 1-14, 16-22 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (applicant's IDS filed 09/13/2004), Olie et al. (Biochimica et Biophysica Acta 1576, 2002), Parrish et al. (applicant's IDS filed 09/13/2004), Matulic-Adamic (applicant's IDS filed 09/13/2004) and Caplen (Expert Opin. Ther. 2003, Vo. 3(4): 575-586).

Claim 1 is drawn to a DFO as interpreted above and further limited wherein the first and second regions are separated by a palindrome sequence, wherein the DFO comprises a 3' terminal cap moiety such as a deoxy abasic moiety or a dinucleotide, wherein the DFO comprises no ribonucleotides, ribonucleotides and modified purines or pyrimidines and drawn to a pharmaceutical composition comprising said DFO.

It must be noted that the word "having" in claim 1 is interpreted as open terminology in light of the specification. Therefore, the limitation of "a first region having nucleotide sequence complementary to nucleotide sequence of a target RNA" is interpreted to mean the first region can include other nucleotide sequences that may not be complementary to the target RNA. Likewise, the limitation of "a second region having nucleotide sequence that is an inverted repeat of the nucleotide sequence in the first region" is interpreted to mean the second region can include nucleotide sequences that are not inverted repeats of the nucleotide sequence in the first region.

Tuschl et al. teach a single stranded oligonucleotide that is capable of forming a double stranded oligonucleotide CGUACGCGG**AA**UACUUGAAAUGUC (as illustrated in Figure 19, last duplex in Figure 19A). Tuschl et al. a single stranded oligonucleotide comprises a region that is complementary to a GL2 luciferase gene (see page 22) and teach the oligonucleotide comprises a second region that comprises sequences that are inverted repeats of a first region (as indicated by the underlined nucleotides). The cited sequence taught by Tuschl et al. comprises a palindrome sequence comprising 2 nucleotides that are between the first region and the second region (as indicated by the bolded nucleotides). Tuschl et al. teach 2'-deoxy thymidine, an abasic moiety, can be substituted for uridine at the 3' ends, i.e. a terminal cap. For example, the nucleotides may be modified at the 2' position of the ribose sugar on either strand, which includes any purine and pyrimidine. Preferred modifications are listed on page 6 and include 2'-O-alkyl and 2' fluoro modifications and Tuschl et al. specifically teach the preferred modifications may be combined in a single siRNA. Tuschl et al. teach a 5'-phosphate

on the antisense strand is required for siRNA function (see page 4, lines 12-20) and teach pharmaceutical compositions comprising double stranded nucleic acids and an acceptable carrier (see page 9, lines 17-25). Tuschl et al. do not explicitly teach the optimum number and placement of 2'-sugar modifications such that siRNA activity is retained. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules and that more extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Thus, Tuschl et al. does recognize that chemical modification of the 2'-OH is an effective variable that may enhance nuclease resistance on the one hand and modulate siRNA activity on the other. Furthermore, Tuschl et al. suggests several types of substituents that may be used to replace the 2'-OH group, namely 2'-O-alkyl substituents (see page 6).

Parrish et al. teach a double stranded nucleic acid comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides (see Figure 5) and further teach this double stranded nucleic acid can mediate degradation of cellular RNA (see abstract page 1082).

Olie et al. teach designing the same oligonucleotide sequence with several different chemical modifications including phosphorothioate and 2'-sugar modifications and teach analysis of said different oligonucleotide sequences to determine the most efficient oligonucleotide sequence.

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68). Matulic-Adamic et al. further teach a double stranded structure comprising separate sense and antisense strands and further wherein this

structure comprises a connecting loop comprising a linker or non-nucleotide linker (see Figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention, and a matter of routine experimentation, to use the general conditions taught by Tuschl et al. for making 2'-modified double stranded oligonucleotides to discover the optimal number and placement of 2'-sugar modifications in any double stranded oligonucleotide, such that the resulting double stranded oligonucleotide was endowed with maximum stability and functionality. Additionally, it would have been obvious to one of ordinary skill in the art to incorporate known modifications, such as 2'-O-methyl, to impart increased stability and functionality in any double stranded oligonucleotide because it is well known to one of skill in the art that modifications of RNA with 2'-O-methyl groups stabilize RNA and can protect RNA from nuclease degradation and one would be motivated to incorporate 2'-O-methyl groups to improve the efficacy of double stranded RNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate terminal cap moieties as taught Matulic-Adamic and into the double stranded oligonucleotide as taught Tuschl et al. Further, it would have been obvious to incorporate 2'-fluoro modifications into said double stranded oligonucleotide to enhance stability and nuclease resistance.

One would have been motivated to create such compounds with increased stability and functionality, and since double stranded oligonucleotides are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function in culture and in whole organisms (paragraphs 29-30), which may be

considered to be nuclease-rich environments. One would therefore be motivated to chemically enhance the double stranded oligonucleotides resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. Further, Tuschl et al. teach 2'-O-methyl modification of both strands of the duplex as well as either sense or antisense strand alone, are not well tolerated (see Figure 14) and therefore one would have been motivated to search for particular chemical modifications that are tolerated by the double stranded RNA by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability and functionality of the double stranded oligonucleotide. Moreover, one would have been motivated to incorporate 2'-deoxy-2'fluoro modifications into said double stranded oligonucleotide because Parrish et al. specifically teach 2'-deoxy-2'fluoro modifications incorporated into double stranded oligonucleotide are compatible with RNAi activity (see page 1081). Further, it would have been obvious to one or ordinary skill in the art to incorporate chemical modifications in all of the nucleotide positions on one or both strands of said double stranded oligonucleotide as part of routine experimentation to further increase the efficacy of double stranded oligonucleotides such as demonstrated by Olie et al. Olie et al. teach an antisense RNA compounds comprising affinity enhancing 2'-sugar modifications in combination with 2'-deoxy modifications and found that inhibition of expression of mRNA is more effective compared to an unmodified RNA molecule. Therefore, Olie et al. provide motivation for modifying any nucleotide of the claimed DFO given that such modifications increased the efficacy of an antisense

oligonucleotide and further given that these modifications have been shown in the art to increase a nucleic acid's cellular uptake, target affinity and resistance to degradation. Further, one would have been motivated to incorporate terminal cap moieties and linker molecules because Matulic-Adamic et al. teach terminal cap moieties provide nuclease resistance and protection from degradation. Since each of the modifications were known to increase efficiency of oligonucleotide delivery and stability, one would have been motivated to incorporate into the oligonucleotides capable of forming a duplex, as taught by Tuschl et al.

The motivation to chemically modify double stranded oligonucleotides is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any oligonucleotide capable of forming a duplex to any gene provided the target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein and

further given that Parrish et al. teach sugar, base and phosphorothioate modifications are well tolerated in dsRNA involved in RNA interference. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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KC
Examiner
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